Ammine/Amine Platinum(IV) Dicarboxylates: A Novel Class of Platinum Complex Exhibiting Selective Cytotoxicity to Intrinsically Cisplatin-resistant Human Ovarian Carcinoma Cell Lines

Lloyd R. Kelland,2 Barry A. Murrer, George Abel, Christen M. Giandomenico, Prakash Mistry, and Kenneth R. Harrap

Drug Development Section, The Institute of Cancer Research, Belmont, Sutton, Surrey SM2 5NG, United Kingdom [L. R. K., G. A., P. M., K. R. H.]; Johnson Matthey Technology Centre, Sonning, Reading, United Kingdom [B. A. M.] and Johnson Matthey Biomédical Research, West Chester, Pennsylvania 19380 [C. M. G.]

ABSTRACT

Using a panel of six human ovarian carcinoma cell lines varying by two orders of magnitude in terms of cisplatin cytotoxicity, we have investigated the in vitro antitumor activity of a series of novel alkylamine ammine dicarboxylatedichloroplatinum(IV) complexes of the general formula c, t, c-[PtCl2((OCOÄ)2NH3( ÄNH2)] with various ligands and substituents. A clear relationship existed between increasing the number of carbons in the R1 substituent and increasing cytotoxicity up to R1 = C7H15. In terms of changing the R2 group, maximum cytotoxic effects were conferred by alicyclic substituents. Furthermore, increasing the alicyclic ring size from cyclobutane through to cycloheptane resulted in increasing cytotoxicity. The agents with longer axial chains (e.g., JM300, R = cyclohexyl, R2 = C6H13) were significantly more cytotoxic than cisplatin and, moreover, exhibited a selective cytotoxic effect against the most intrinsically cisplatin-resistant cell lines (e.g., for HX/62, cisplatin 50% inhibitory concentration, 12.6 μM; SKOV-3, cisplatin 50% inhibitory concentration, 4.4 μM and 41 μM; cisplatin 50% inhibitory concentration, 0.23 μM; JM300 was 840-, 440-, and only 34-fold more active, respectively). The dicarboxylates JM221 (R = cyclohexyl, R2 = C6H13) and JM244 (R = n-propyl, R2 = C6H13) also retained activity against a 4-fold cisplatin-acquired resistant variant of the 41M cell line. At least part of the increased cytotoxicity of the dicarboxylate, JM221, over cisplatin appeared to be attributable to an increased intracellular accumulation. This novel class of platinum compound represents a valuable lead in the development of a "third-generation" agent capable of exhibiting activity against clinical disease currently resistant to cisplatin.

INTRODUCTION

The introduction of the square-planar complex cisplatin [cis-diaminocyclohexan platinum(II)] has resulted in dramatic improvements in the response rate for some tumor types, notably testicular teratoma and ovarian carcinoma (1, 2). While the unfavorable toxicity profile of cisplatin (primarily nephrotoxicity) has been overcome by the development of the second-generation agent, carboplatin (3–5), there remains an unquestionable need for further platinum drugs which circumvent resistance. As with other cancer chemotherapeutic agents, cellular resistance to the clinically used platinum agents, cisplatin and carboplatin, represents a major clinical limitation to their efficacy (6–8). Indeed, a recent United States survey has revealed that, of approximately 18,000 new ovarian cancer cases diagnosed per annum, two thirds will ultimately die of their disease (9). Recent clinical data have shown a low (around 6%) statistically nonsignificant incidence of non-cross-resistance between cisplatin and carboplatin, suggesting that these two agents are effective against essentially the same population of tumors (10, 11). Moreover, a similarly low level of non-cross-resistance among cisplatin, carboplatin, and iproplatin has been reported (12, 13).

Tumor cell resistance to cisplatin/carboplatin may either be present at the onset of treatment (intrinsic) or be acquired during successive treatments. Laboratory-based biochemical studies, using a variety of murine and human tumor models, point to a multifocal basis for resistance to platinum drugs involving one or more of transport, intracellular detoxification, chromatin binding, and DNA repair mechanisms (14, 15). Furthermore, it is largely unclear whether intrinsic resistance and acquired resistance are due to similar or dissimilar mechanisms.

To date, there has been a notable paucity of novel platinum chemistry addressing the issue of resistance. Perhaps the only prominent contribution thus far, in over 20 yr of study, has been the discovery of the 1,2-diaminocyclohexane/heptane carrier ligand (16). These DACH complexes retain activity in cisplatin-acquired resistant murine leukemias, both in vitro (17, 18) and in vivo (19). However, using tetraplatin [(trans-d,l)-1,2-diaminocyclohexane tetrachloroplatinum(IV)], previous studies in this Department have shown no activity against another cisplatin-acquired resistant murine model (the ADJ/PC6 plasmacytoma) (20). Moreover, across 16 human ovarian carcinoma xenografted tumors, only two were sensitive to tetraplatin, these being the same tumors which were particularly sensitive to cisplatin and carboplatin (21). At present the clinical relevance of the DACH carrier ligand in platinum complexes is largely untested. Some DACH complexes [e.g., 1,2-diaminocyclohexane(4-carboxyphthalato)platinum(II), JM82] and the closely related TN0–6 [1,1-diaminomethylenecyclohexane sulphato platinum(II)] have entered Phase I/II clinical trials but have subsequently been dropped, primarily due to unacceptable toxicity (22–25). Currently, two more water-soluble DACH complexes, oxalatiplatin [1,2-diaminocyclohexane oxalatoplatinum(II)] (26) and tetratapl (27) are undergoing early clinical evaluation.

Our platinum-based drug discovery program, is aimed at developing drugs capable of broadening the clinical spectrum of activity of cisplatin/carboplatin through circumvention of cisplatin resistance. To assist in these objectives we have established human ovarian tumor models [both in vitro (28) and in vivo (21)] containing examples of both intrinsic and acquired resistance to cisplatin. In the present study, a subpanel of the in vitro cell lines has been used to evaluate the cytotoxic properties of a novel class of platinum(IV) complex, namely, ammine/amine dicarboxylates.

Received 9/5/91; accepted 12/3/91.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 This study was supported by grants to the Institute of Cancer Research from the Cancer Research Campaign and the Medical Research Council, the Johnson Matthey Technology Centre, and Bristol Myers Squibb Oncology.

2 To whom requests for reprints should be addressed.

822

Downloaded from cancerres.aacrjournals.org on July 21, 2017. © 1992 American Association for Cancer Research.
MATERIALS AND METHODS

Cell Lines

Six "parent" human ovarian carcinoma cell lines have been used. SKOV-3 (29) and OVCAR-3 (30) were obtained from the American Type Culture Collection. Establishment details and biological properties of the other four cell lines (HX/62, PXN/94, CH1, and 41M) have been described previously (28). In addition, acquired resistance to cisplatin has been developed in the 41M cell line by continuously exposing cells to increasing concentrations of drug (up to a maximum of 1 µM) over a 15-mo period. A cell line, 41McisR, was approximately 6-fold resistant to cisplatin in IC_{50} terms when compared with the parent line.

All seven cell lines grew as monolayers in Dulbecco's modified Eagle's medium containing 10% fetal calf serum (Imperial Laboratories, Andover, United Kingdom). Details of the synthesis of these agents have been described recently (31). The generalized structure of the platinum(IV) dicarboxylates and the structures of other platinum agents used in this study are shown in Fig. 1.

Assessment of Cytotoxicity

Platinum agents were dissolved immediately before use in 0.9% saline (for cisplatin, JM118, and JM149) or water (for carboplatin) or absolute ethanol [for the platinum(IV) dicarboxylates]. Where ethanol was used, the final concentration of solvent in the growth medium was 0.5%; this concentration had no growth-inhibitory effect and, moreover, the cytotoxicity of cisplatin was unaltered.

Three independent methods of assessing cytotoxicity were adopted. In all cases, cell lines were used within a defined passage range of 20; during this period no differences in population doubling time or morphology were apparent for any of the lines.

Clonogenic Assay. The colony-forming assay was performed as described previously (32). Briefly, single cells, harvested using a 5-min treatment with 0.25% trypsin and 0.02% EDTA, were seeded into triplicate 25 cm² tissue culture flasks, each containing 4.5 ml of growth medium. After overnight attachment at 37°C, cells were exposed to varying concentrations of platinum agent (added in 0.5 ml as a 10× concentrate). After 10 to 12 days, the flasks were washed with PBS and stained for 10 min using 0.5% methylene blue in 50% methanol/water, and colonies containing greater than 50 cells were counted by eye. Under these conditions the SKOV-3 cell line typically gave colony-forming efficiencies in the region of 30%.

Tritiated Thymidine Incorporation Assay. This was performed essentially as described previously (28). Single viable cells were seeded at between 5 x 10^3 and 1 x 10^4 cells per well in 96-well microtiter plates in 200 µl of growth medium. Agents were added the following day in triplicate wells for a total exposure time of 96 h unless otherwise indicated. Where the effect of time of exposure of agents was being assessed, at the end of the appropriate exposure period, plates were washed twice with PBS and then with growth medium. Fresh growth medium (200 µl) was then added to each well, and cells were incubated to 96 h after initial addition of the agent. [methyl-³H]Thymidine (4.2 µCi/ml; specific activity, 5 Ci/mm) was then added to each well for 60 min, and cytotoxicity was assessed as described before (28).

SRB Assay. Cytotoxicity was assessed as for the thymidine incorporation assay except that, at the end of the 96-h exposure period, basic amino acid content was analyzed using 0.4% SRB in 1% acetic acid (Sigma Chemicals). The staining protocol has been described previously (33). All results represent the means of at least three independent experiments.

Platinum Accumulation Measurements

Accumulation studies were performed with cisplatin [cis-diammine-dichloroplatinum(II)] and JM221 [(ammine dibutycarboxylomethylamino)cyclohexylamine] using the SKOV-3 cell line. Agents were added for 2 h at various concentrations to approximately 3 x 10^5 cells growing exponentially. Immediately after exposure, cell monolayers were washed 3 times with ice-cold PBS, scraped, and harvested in 0.5 ml of PBS. Samples, held on ice, were then sonicated (Soniprep 150; Fisons, Loughborough, United Kingdom). Total intra-cellular platinum content was then determined by flameless atomic absorption spectroscopy (Perkin Elmer Model 1100B and HGA700). Protein content was analyzed according to the method of Lowry et al. (34). Cellular platinum levels were expressed as nmol of platinum/mg of protein.

RESULTS

Cytotoxicity determinations for cisplatin, carboplatin, JM118, JM149, and three ammine/amine platinum(IV) dicarboxylates (JM221, R = cyclohexyl, R₁ = n-CAH₃; JM274, R = cyclohexyl, R₁ = n-C₆H₅; JM244, R = n-propyl, R₁ = C₆H₅) against a panel of six human ovarian carcinoma cell lines are shown, using the sulforhodamine B assay (Fig. 2). It is apparent that, for all six lines, the three ammine/amine platinum(IV)
dicarboxylates confer substantially greater cytotoxicity than the other compounds, including cisplatin.

Structure-Activity Relationships. We have investigated the effect on cytotoxicity of substitutions of both the R (amine) and R\(_1\) (axial) ligands using the sulforhodamine B assay. Table 1 shows the effect of various amine ligand substitutions for a series of complexes where the axial ligand is acetato (R\(_1\) = CH\(_3\)). Examples of straight- and branched-chain aliphatic, alicyclic, and aromatic groups are included. The table identifies the following features: (a) the parent diammine (JM211) was significantly less cytotoxic than the mixed amine complexes where R = aliphatic or alicyclic; (b) for the mixed amine complexes, cytotoxicity increased from aromatic (e.g., JM281 and JM285), to straight chain aliphatic (JM189), to branched chain aliphatic, through to alicyclic groups conferring greatest cytotoxicity; (c) for the alicyclic mixed amines where R varied from cyclobutyl (JM236) to cycloheptyl (JM269), cytotoxicity generally increased with each stepwise increase in alicyclic ring size.

Table 2 shows a similar series of complexes where R\(_1\) = n-
corresponding R substitution, for the acetato complexes shown of carbons present in both of the axial chains of a series of ammine/amine C3H7; i.e., the axial ligand is butyrato. On comparison with the and c-C2H7, c-C5H9, c-C6Hn, mean I< ." calculated for the six ovarian carcinoma cell lines) and the total number an average of 14-fold more cytotoxic across the six cell lines in Table 1, it is clear that the butyrates confer greater cytotox carbon complexes. (Table 1) are retained for the butyrates. Again, complexes possessing an alicyclic ring (particularly cyclohexyl and cyclo- ship between increasing cytotoxicity and increasing number of ligands, the butyrate was more cytotoxic than the acetate has been extended in Fig. 3. The figure shows the relationship between IC50 and the total number of carbons present in the axial chain complexes for compounds where the amine (R) ligand is an alicyclic ring (i.e., C4 to C7). There is a demonstrable relation between increasing cytotoxicity and increasing number of axial carbons up to a total of 12 (where R1 = C6H11). Longer axial chain complexes confer similar cytotoxicity to the 12-carbon complexes. C2H7; i.e., the axial ligand is butyrato. On comparison with the corresponding R substitution, for the acetato complexes shown in Table 1, it is clear that the butyrates confer greater cytotoxicity (e.g., where R = cyclohexyl, JM221, the dibutyrato, was an average of 14-fold more cytotoxic across the six cell lines than was JM216, the corresponding diacetate). Otherwise, the structure-activity relationships observed with the acetato complexes (Table 1) are retained for the butyrates. Again, complexes possessing an alicyclic ring (particularly cyclohexyl and cyclo-heptyl) confer the greatest cytotoxicity.

The observation from Tables 1 and 2 that, for identical amine ligands, the butyrate was more cytotoxic than the acetate has been extended in Fig. 3. The figure shows the relationship between IC50 and the total number of carbons present in the axial groups for compounds where the amine (R) ligand is an alicyclic ring (i.e., C4 to C7). There is a demonstrable relationship between increasing cytotoxicity and increasing number of axial carbons up to a total of 12 (where R1 = C6H11). Longer axial chain complexes confer similar cytotoxicity to the 12-carbon complexes.

Effect of Exposure Time on Cytotoxicity. Fig. 4 shows the effect of alterations in the time of exposure on cytotoxicity (IC50) for cisplatin and JM221 in two cell lines, the intrinsically cisplatin-resistant SKOV-3 line and 41M, a line relatively sensitive to cisplatin.

These data were obtained using the [3H]thymidine incorporation assay. Results show that, at all time points, JM221 was more cytotoxic than cisplatin; even after only a 3-h exposure, for SKOV-3, it is 7 times more cytotoxic. In addition, there appears to be a greater divergence in the two curves for SKOV-3 compared with 41M, indicative of a relatively increased effect of JM221 on SKOV-3. After 96-h exposure, JM221 is 84 times more cytotoxic than cisplatin to the SKOV-3 line but only 10 times more potent in 41M cells.

Selective Enhancement of Cytotoxicity by Platinum(IV) Ammine/Amine Dicarboxylates to Intrinsically Cisplatin-resistant Cell Lines. The apparent selective cytotoxicity to the SKOV-3 cell line by JM221, observed in Fig. 4, has been investigated further by comparing IC50 values for cisplatin and a number of dicarboxylates for all six ovarian carcinoma cell lines. Table 3 shows such a comparison for experiments obtained by both the [3H] thymidine incorporation and sulforhodamine B assays.

Also included are data for JM118 and JM149. A feature observed with both assays is the selective cytotoxicity of the dicarboxylates (JM221, JM274, JM300, and JM244) to the most intrinsically cisplatin-resistant cell lines, HX/62 and SKOV-3. This is particularly apparent on comparison of enhancement factors for HX/62 and SKOV-3 with 41M. For example, for results obtained by the sulforhodamine assay and JM300 (R = c-C4H7, R1 = C3H7), enhancement factors of 840 and 440 were obtained for the HX/62 and SKOV-3 lines, respectively, whereas for 41M, the value was only 34. The selective cytotoxic effects, although still substantial, were not as pronounced with the second, relatively sensitive line, CH1, as with 41M.

Cytotoxicity of JM221 as Assessed by Colony-forming Assay. The in vitro potency of the platinum(IV) ammine/amine dicarboxylates observed with the short-term (4-day) [3H]thymidine and SRB assays has been confirmed using a colony forming end point. As neither the [3H]thymidine incorporation assay (which measures ongoing DNA synthesis) nor the SRB assay (which measures cellular basic amino acid content) at 4 days post-agent exposure distinguishes between viable and doomed cells, it was important to ensure that the effects observed with the platinum(IV) dicarboxylates were also apparent using a full 12-day clonogenic cell survival end point. Fig. 5 shows full survival curves for the SKOV-3 line for continuous exposure to cisplatin and JM221. As for the other assays, the dicarboxylate was evidently more cytotoxic; the IC50 values were 1.2 ¿IM for cisplatin and 0.02 ¿IM for JM221 (enhancement factor of 60).

Activity of Platinum(IV) Ammine/Amine Dicarboxylates against a Cisplatin-acquired Resistant Cell Line. Fig. 6 shows resistance factors (IC50 acquired resistant line/ IC50 parent line) for the pair of 41M cell lines. 41McisR was approximately 4-fold resistant to cisplatin and showed cross-resistance (2.8-fold) to carboplatin. The two dicarboxylates, however, (JM221 and JM244) both circumvented cisplatin acquired resistance in this model producing resistance factors lower than 1 (0.61 and 0.56, respectively).

Intracellular Accumulation of JM221 versus Cisplatin. As a preliminary insight into the possible mechanistic reasons for
IN VITRO CYTOTOXICITY OF NOVEL PLATINUM COMPLEXES

Table 3 Comparison of IC₅₀ values for cisplatin and dicarboxylates for six ovarian carcinoma cell lines using [³H]thymidine incorporation and SRB assays

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Cisplatin IC₅₀ (µM)</th>
<th>JM118</th>
<th>JM149</th>
<th>JM221 ((R = c-C₆H₁₄, R₁ = C₃H₇))</th>
<th>JM224 ((R = c-C₆H₁₄, R₁ = C₃H₇))</th>
</tr>
</thead>
<tbody>
<tr>
<td>HX/62</td>
<td>2.4</td>
<td>3.8</td>
<td>45</td>
<td>105</td>
<td>84</td>
</tr>
<tr>
<td>SKOV-3</td>
<td>4.4</td>
<td>1.5</td>
<td>44</td>
<td>105</td>
<td>44</td>
</tr>
<tr>
<td>PXN/94</td>
<td>3.0</td>
<td>1.1</td>
<td>36</td>
<td>115</td>
<td>273</td>
</tr>
<tr>
<td>OVCAR-3</td>
<td>0.64</td>
<td>0.4</td>
<td>13</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>41M</td>
<td>0.04</td>
<td>1.0</td>
<td>10</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>CH1</td>
<td>0.13</td>
<td>3.2</td>
<td>87</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

Enhancement factor

<table>
<thead>
<tr>
<th>SRB assay</th>
<th>Cisplatin IC₅₀ (µM)</th>
<th>JM118</th>
<th>JM149</th>
<th>JM221 ((R = c-C₆H₁₄, R₁ = C₃H₇))</th>
<th>JM274 ((R = c-C₆H₁₄, R₁ = C₃H₇))</th>
<th>JM300 ((R = c-C₆H₁₄, R₁ = C₃H₇))</th>
<th>JM244 ((R = n-C₆H₁₄, R₁ = C₃H₇))</th>
</tr>
</thead>
<tbody>
<tr>
<td>HX/62</td>
<td>12.6</td>
<td>4.8</td>
<td>0.4</td>
<td>45</td>
<td>105</td>
<td>84</td>
<td>126</td>
</tr>
<tr>
<td>SKOV-3</td>
<td>4.4</td>
<td>2.1</td>
<td>0.32</td>
<td>44</td>
<td>105</td>
<td>44</td>
<td>65</td>
</tr>
<tr>
<td>PXN/94</td>
<td>3.0</td>
<td>1.8</td>
<td>1.4</td>
<td>36</td>
<td>115</td>
<td>273</td>
<td>64</td>
</tr>
<tr>
<td>OVCAR-3</td>
<td>0.64</td>
<td>1.1</td>
<td>0.11</td>
<td>13</td>
<td>18</td>
<td>58</td>
<td>19</td>
</tr>
<tr>
<td>41M</td>
<td>0.23</td>
<td>0.7</td>
<td>0.06</td>
<td>4.2</td>
<td>16</td>
<td>34</td>
<td>13.5</td>
</tr>
<tr>
<td>CH1</td>
<td>0.10</td>
<td>2.1</td>
<td>0.15</td>
<td>16</td>
<td>66</td>
<td>67</td>
<td>33</td>
</tr>
</tbody>
</table>

* IC₅₀ cisplatin/IC₅₀ Pt agent.

**DISCUSSION**

A novel class of platinum(IV) complex, the ammine/amine platinum(IV) dicarboxylates, has been evaluated for antitumor activity against a panel of human ovarian carcinoma cell lines varying by two orders of magnitude in their sensitivity to cisplatin. Some of the dicarboxylates, notably those containing a total of at least 8 carbons in their axial ligands, exhibited particularly dramatic in vitro cytotoxicity properties. (a) In terms of potency, these agents were at least 100 times more cytotoxic than cisplatin. This has been confirmed by three independent cytotoxicity assays. (b) They appeared to exert some selectivity in their antitumor effects against the most intrinsically cisplatin-resistant cell lines (HX/62 and SKOV-3). Effectively, the longer axial chain dicarboxylates enhanced the sensitivities of the highly cisplatin-refractory HX/62 and SKOV-3 cell lines to levels above those of cisplatin in the highly sensitive 41M and CH1 lines. As platinum analogues to date have been hard pressed to match the cytotoxicity of cisplatin itself, let alone exceed it, these complexes are of exceptional interest. Moreover, the dicarboxylates were able to circumvent acquired resistance to cisplatin in the 41M cell line.

A further feature of members of the ammine/amine platinum(IV) dicarboxylate class of complex is that they may be chemically modified at a number of sites. For example, substitutions in the amine, trans-axial ligands, and leaving groups are possible. The structure-activity relationships investigated in this study have shown that the dramatic cytotoxicity effects are mediated largely through the lipophilicity of the axial ligands. However, cytotoxicity may also be mediated, but to a lesser degree, through alterations in the amine ligand. In particular, alicyclic, rather than aliphatic or aromatic, substitutions produced the greatest cytotoxic effects. Furthermore, within the alicyclic series, cyclobutane, -pentane, -hexane, and -heptane, cytotoxicity increased with each step up in ring size. To date, the effect of varying the dichloro leaving groups has not been investigated.

In order to assess fully the potential of this class of agent as a broader spectrum platinum drug, it is desirable to elucidate the mechanistic basis for the observed potency and selectivity effects. It is widely accepted that cisplatin exerts its cytotoxicity through binding to DNA (35). However, as the ammine/amine dicarboxylates are platinum(IV) complexes, previous studies with other platinum(IV) complexes would suggest that they are essentially inert to ligand substitution. For example, studies with cis-dichloro-trans-dihydroxy-bis-isopropylamine platinum(IV) (iproplatin) have identified the divergent cis-dichloro-
observed cytotoxicity effects may be attributable to the enhanced lipophilicity of JM221, facilitating platinum transport into the cell. As reported previously (31), JM221 has an octanol/water partition coefficient of 41 versus <0.0001 for cisplatin. Thus, the dicarboxylates may be acting as prodrugs enabling a more effective intracellular delivery whereupon reduction to reactive platinum(II) species (including JM118) occurs. Although some reduction to platinum(II) species might occur in vivo prior to transport into tumor cells, these in vitro data highlight the enormous sensitivity of tumor cells to platinum if it can be delivered to critical cellular targets. Further studies are needed to elucidate the mechanistic basis for their selectivity toward intrinsically cisplatin-resistant cell lines. As one of the probable metabolites, JM118, does not show any such selective cytotoxicity (Table 3), then this exciting property must be due either to an alternative metabolite or to a property of the parent dicarboxylate itself. It appears possible that some tumor cell-selective transport, metabolism, or DNA binding/repair mechanism might be involved.

In summary, the potency and selectivity toward intrinsically cisplatin-resistant cell lines exhibited by this novel class of platinum complex suggest that it provides a valuable lead in the search for new broad-spectrum platinum drugs. Further studies are warranted to determine their activity in vivo in the cisplatin resistance setting and to elucidate whether the selectivity effects are mediated via tumor-dependent metabolism. As the basic structure of this novel class of platinum(IV) complex is readily amenable to chemical modification, it might be possible to further refine the enhanced selectivity effects and delineate tumor cell cytotoxicity from host toxicity.

ACKNOWLEDGMENTS

Our thanks are due to A. Ford and J. North for the efficient preparation of the manuscript.

REFERENCES


Ammine/Amine Platinum(IV) Dicarboxylates: A Novel Class of Platinum Complex Exhibiting Selective Cytotoxicity to Intrinsically Cisplatin-resistant Human Ovarian Carcinoma Cell Lines

Lloyd R. Kelland, Barry A. Murrer, George Abel, et al.


Updated version Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/52/4/822

E-mail alerts Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.